REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.111. Reconsideration of the claims in view of the above amendments and following remarks is respectfully requested.

At the outset, Applicants would like to thank Examiner Hama for the courtesy of the personal interview held December 13, 2007, which helped clarify and further prosecution of the instant application.

1. Status of the Claims

Claims 1-19, 11-13, and 45-47 stand pending and rejected. Claims 10, 14-44, and 48 stand previously canceled.

After entry of the above amendments, claims 1, 2, 4, 11 and 45-47 stand amended. Support for the claim amendments can be found for example in the original claims, on page 34 (for "increased"), and page 149 (stable integration in to the genome). Thus, Applicants believe no prohibited new matter has been introduced by entry of the above amendments. Amendments are made without disclaimer of or prejudice to the canceled subject matter. Applicants reserve the right to file a continuation application on any subject matter canceled by way of amendment.

2. Information Disclosure Statements

Applicants note with appreciation the acknowledgement of the Information Disclosure Statement filed June 12, 2007. Applicants appreciate the Examiner's clarifying comments regarding the Schneider and Corseaux references.

3. Double Patenting Rejection

Applicants note with appreciation that the double patenting rejection of claims 1-9, 11-13, and 45-47 has been withdrawn.

4. Rejection Under 35 U.S.C. § 112, First Paragraph

Applicants note with appreciation that the rejection of claims 1-9, 11-13 and 45-47 as lacking written descriptive support has been withdrawn.

The enablement rejection has been withdrawn in part. In light of the amendments that the mice exhibit a phenotype, the rejection has been withdrawn. Office Action, page 8.

5. Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-9, 11-13, and 45-47 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for "a transgenic mouse comprising its genome, a transgene construct comprising SEQ ID NO: 4 operably linked to CMVbactin or rat type I collagen promoter, wherein said transgenic mouse has increased bone density, does not reasonably provide enablement for a transgenic mouse having somatic and germ cells comprising a nucleic acid which comprises any promoter region that directs protein expression in said transgenic mouse cells that is operably linked to a sequence encoding SEQ ID NO: 4 or a sequence encoding a mouse LRP5 protein having a glycine 170 to valine substitution, and wherein said transgenic mouse has increased bone density." Office Action, page 4. On page 5, the Office goes on to allege that the rejection is of the use of any promoter, with three issues relating to the promoter: (1) any promoter is directed to tissue specific promoters not related to bone, (2) the unpredictability in using tissue-specific promoters from heterologous animals; (3) the predictability of the promoter in the claimed mice. Office Action, pages 5-6.

Bone Specific Promoters

Applicants traverse the rejection. First, the nature of the rejections are not set forth with respect to each of the claims. Claims 1-9, 11-13, and 45-47 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. With regard to tissue specific promoters, claims 5, 6, 8, and 46 recite a bone specific promoter, and therefore are not the subject as to this aspect of the rejection. Additionally, the Office admits that CMVβActin promoter is enabled. Thus, claim 7 also is free of the rejection.

The Office then says that "the claims broadly read as though expression of LRP5 in tissues other than bone (e.g. cartilage or muscle) would result in the bone mass phenotype. However, neither the art nor the specification provide guidance that LRP5 or HBM expressed in other tissue...results in transgenic mice that exhibit an increased bone mass. As such, the claimed invention is limited such that the phenotype occurs when the transgene construct is expressed in bone." Office Action, page 5.

With regard to the above paragraph, expression in bone is stated in claim 2, therefore, claim 2 cannot be rejected under this argument. Applicants have amended claims 1, 4 and

46 to recite "bone cells" (and all their dependent claims as well). Thus, the issue of whether other tissues could possibly be construed as responsible for the increase in the bone mass phenotype stands mooted. Accordingly, this argument in support of lack of enablement is obviated with respect to remaining claims, 1, 3-4, 9, 11-13, 45 and 47.

Unpredictability of Bone Specific Promoters

On page 5, the Office alleges that the scope of the bone-specific promoters is unenabled. The Office asserts that "there is unpredictability in using tissue-specific promoters from heterologous animals." The Office relies upon Cowan et al., 2003 *Xenotransplantation* 10:223-231 for the premise that it teaches promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. The authors found that the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The Office then extrapolates that based on Cowan's teaching one cannot reasonably predict that tissue-specific promoters behave predictably in transgenic animals. Office Action, page 6.

Applicants traverse the logic of the argument, and thereby the Office's conclusion that the claims lack enablement. Applicants point out that the specification as a whole and what was known in the art at the time must be considered. Additionally, what the cited art teaches as a whole must also be considered. *See In re Angstadt*, 190 U.S.P.Q. 214, 219-220 (C.C.P.A. 1976); *see also* M.P.E.P. § 2164.05 ("Determination of Enablement Based on Evidence as a Whole").

Cowan is directed to expression of human complement regulatory proteins (hCRPs) using human promoters of three human genes, intercellular adhesion molecule 2 (ICAM-2), platelet endothelial cell adhesion molecule 1 (PECAM-1) and endoglin. *See* Abstract, Cowan. Cowan also relates to endothelial targeting of protein expression. Applicants herein are not targeting endothelial expression of the DNAs and proteins. The instant claims relate to bone expression in a transgenic animal. Additionally, Applicants are not expressing the subject genes and proteins in pigs. Rather, these animals express a human gene in mice. Applicants assert that the application of Cowan's teachings, when viewed *as a whole*, are not relevant. Cowan does not contemplate the instant gene-animal-disease model combination. Cowan has been improperly extrapolated to a scientific scope that lacks scientific support.

The Office then asserts that "the specification does not provide guidance that bone-specific promoters from heterologous species of animals can be used to arrive a the claimed invention. As such the claims are limited to rat type I collage [*sic*] promoter." Office Action, page 6. Applicants disagree. Applicants have working models of mice that express the human HBM or the human Zmax1, which produces an animal with increased in bone mass. There is high identity between LRP5 as between mouse and human, especially with respect to the area in which the G171→V mutation occurs. (*See* Fig. 26A) Applicants assert that given the sequence identity, conservation of sequence, and the complete lack of correlation as between Cowan's teachings for this particular gene-animal-model disease combination, no *prima facie* showing of lack of enablement as been adduced as with regard to bone specific promoters from heterologous animals. However, in an effort to further prosecution, Applicants have amended claims 1, 2, 4, 46, and 47 to recite a murine or viral promoter.

Predictability of Promoter Activity

The Office then relies upon Xu (2001, *Gene* 272: 149-156) for the premise that there are differences in promoter activity in different cell types. The Office admits that the specification provides teaching as to the usage of CMVbActin and rat type I collagenase promoters. However, the Office asserts that the specification does not provide guidance that other promoters can drive expression of HBM, such that the mice exhibit the phenotypes described in the specification.

Applicants have amended the claims to recite viral or murine promoters. Thus, "any promoter" is no longer contemplated. With regard to viral promoters, these have long been used to express a variety of genes. As discussed in Xu, the CMV promoter is regarded as one of the strongest. RSV is also a successful promoter. Thus, Applicants assert that no scientific argument has been adduced for why viral promoters would not drive expression of HBM or Zmax in mice. Without a *prima facie* case of enablement adduced, the rejection as to viral promoters should be withdrawn (all claims as amended). Applicants further note that the claims have been amended to recite a murine promoter. During the interview, the Examiner mentioned that the bone promoters are enabled. No art could be identified to assert otherwise, and the Supervisory Patent Examiner also indicated to the Examiner that the bone promoters were enabled. Thus, prior arguments by the Office as to limiting only to the one promoter is deemed mooted. Additionally, as predictability exists, Applicants submit this argument fails to support the enablement rejection for the amended claims.

Overexpression of human v. mouse proteins

Next, the Office rejected the claims as lacking enablement, because allegedly "an artisan cannot predict that the phenotype exhibited by a transgenic mouse overexpressing human protein would necessarily result in the same phenotype as a transgenic mouse overexpressing the mouse protein." Office Action, page 7. The Office relies on Vaisman et al., 2001, *J. Clin. Invest.* 108: 303-309 for allegedly teaching that there are differences in *in vivo* function of LCAT in transgenic mice that overexpress the mouse versus the human protein. Thus, the artisan cannot reasonably predict that the mouse proteins have the same activity as a human protein in transgenic animals.

Applicants disagree with the Office's interpretation and application of the paragraph on page 308 of Vaisman. Applicants reiterate below the paragraph, which bridges pages 307-308:

> Cavelier et al. (38) recently reported the generation of two different transgenic mouse lines from BACs containing the hABCA1 gene. In contrast to our findings, they reported that mice with increased hABCA1 expression in liver (twofold; determined by quantitative RT-PCR) and macrophages (twofold; determined by increased cholesterol efflux) or testis had no changes in the plasma lipids or in HDL-C levels. In the present study, hABCA1 expression was increased four- to nine-fold in liver and three- and sixfold in macrophages in hABCA1-Tg mice. Thus, lower hABCA1 expression levels may account for the lack of increased plasma HDL concentrations in transgenic mice generated using hABCA1 BACs (38). These authors have suggested (38) that interaction between human ABCA1 and endogenous mouse ligands may be inefficient requiring higher levels of expression to alter the plasma lipid profile. Differences in in vivo function of LCAT have been reported in transgenic mice overexpressing the mouse versus the human enzyme (29, 39).

What the authors report is a lower expression of human genes in the mouse. Here, Applicants have working examples of the human gene in mice. The likelihood that the mouse gene would not similarly operate to increase bone mass if over expressed or if it has the G170→V mutation is not rationally supported by Vraisman. When viewed for what it teaches as a whole, the scientific data presented by Vraisman does not support the argumentation and rationale of the Office. Applicants submit that no *prima facie* demonstration of why the mouse gene, when over expressed or when using the homologous mutation of G170→V, would not result in an increased bone mass in mice, let alone an argument supported by reasonable scientific evidence. The rejection should be withdrawn.

Modulation

The Office objects to the use of the word "modulation". This has been mooted with the amendment to claims 2, 4, 11, and 46 to recite "increased".

Mouse homolog

The Office asserts on page 8 of the Office Action that the specification does not provide guidance to use a mouse LRP5 protein having a glycine 170 to valine substitution.

Applicants disagree with the Office's conclusion. It is unclear from the Office's argument as to what arguments support its finding for lack of guidance (a conclusory comment in the Office Action referring to previous comments made in the Office Action do not clarify the basis of the rejection). Applicants point out that there is sequence identity between the mouse and human LRP5 protein sequences. Figure 26A compares the mouse and human LRP5 sequences and demonstrates the high degree of identity in the region around residue 170/171. Three dimensional analysis is discussed at least on page 46 of the specification. Specifically, the G171→V mutation occurs on the outer or top surface of the domain of blade 4 of propeller 1. This three dimensional structure would be the same for the mouse sequence. Thus, the Office's allegations that there is insufficient guidance provided regarding the mouse sequence given the sequence analysis, three dimensional analysis, and working examples of animals expressing both the human HBM and human LRP5 sequences is simply unsupported. This aspect of the rejection should be withdrawn.

Episomal Expression

The Office maintained the enablement rejection with respect to stable integration of the construct in to the mouse genome. *See* Office Action, pages 8-10.

Applicants traverse this aspect of the rejection. Again, the Office has not discussed how the rejection applies to each of the rejected claims. For examples, claims 12 and 13 discuss a transgenic mouse that passes to its offspring the transgene construct. To do this, the construct is stably integrated. Thus, claims 12-13 cannot be rejected under this allegation.

The remaining claims implicity impute that the gene is stably integrated because both the "somatic and germ cells" must express have amended the claims to reflect stable integration. The Office's point that the art teaches that unintegrated copies of the microinjected transgene are degraded within four to five days makes the point that to have a high bone mass phenotype, by definition, the animals would have stable expression. Stable expression is implicit in the claims. Thus, the rejection should be withdrawn, even absent the additional amendment to reflect stable integration.

Grafted Cells and Xenotransplantation

The Office next rejects all the claims, because they allegedly read on a transgenic rodent comprising a transplant, wherein the transplant comprises cells with a transgene construct. Office Action, pages 11-13.

Applicants traverse the rejection to the extent it applies to the claims as amended. First, the Office does not indicate to which claims this particular aspect applies. Certainly, claims 12 and 13 would not apply to the xenotransplanted animals or grafted animals, because the nucleic acid is transmitted to the offspring. Secondly, there is stable integration of the construct and stable expression in both the somatic cells and the germ cells. Thus, Applicants assert this argument in support of the lack of enablement rejection also stands mooted, both with the amended claims as well as the previously pending claims.

In view of the above arguments and amendments to the claims, applicants submit that the enablement rejection should respectfully be withdrawn and the claims allowed.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited. In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

If any fees are required, the Office is asked to charge Deposit Account No. 50-0573. The Office can credit any overpayments to the Account.

Respectfully submitted,
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